Association between alcohol consumption and incidence of dementia in current drinkers: linear and non-linear mendelian randomization analysis

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Summary

Background Previous conventional epidemiological studies found a J-shape relationship between alcohol consumption and dementia, but this result was subject to confounding biases and reverse causation. Therefore, we aimed to investigate the potential linear or non-linear causal association between alcohol consumption and the incident risk of dementia in current drinkers.

Methods This study used data from the UK Biobank to investigate the relationship between alcohol consumption and dementia risk. 313,958 White British current drinkers, who were free of dementia during 2006–2010, were followed up until 2021. Alcohol consumption was self-reported and calculated according to the National Health Service guideline. The primary outcome was all-cause dementia identified through hospital and mortality records. We used multivariable Cox models with restricted cubic splines for conventional analysis and both non-linear and linear Mendelian Randomization (MR) analyses to assess causal relationships, employing a genetic score based on 95 SNPs identified from a meta-genome-wide association study of 941,280 people from Europe.

Findings 313,958 current drinkers consumed an average of 13.6 [IQR: 7.1–25.2] units/week alcohol (men averaged 20.2 [11.1–33.9] units/week and women 9.5 [5.3–16.7] units/week). During a mean follow-up of 13.2 years, 5394 (1.7%) developed dementia. Multivariable Cox model with restricted cubic spline functions identified a J-shaped relationship between alcohol consumption and dementia risk, with the lowest risk at 12.2 units/week. The non-linear MR failed to identify a significant non-linear causal relationship (p = 0.45). Both individual-level (HR: 2.22 95%CI [1.06–4.66]) and summary-level (1.89 [1.53–2.32]) linear MR analyses indicated that higher genetically predicted alcohol consumption increased dementia risk.

Interpretation This study identified a positive linear causal relationship between alcohol consumption and dementia among current drinkers. The J-shaped association found in conventional epidemiological analysis was not supported by non-linear MR analyses. Our findings suggested that there was no safe level of alcohol consumption for dementia.

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Keywords: Alcohol consumption; Dementia; Mendelian randomization

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Research in context

Evidence before this study

Previous conventional epidemiological studies found a J-shape relationship between alcohol consumption and dementia, but this result was subject to several biases. Mendelian randomization (MR) analysis in genetic epidemiology studies, is similar to a "genetic randomized control trial" due to the random allocation of genotypes from parents to offspring, and thus, not affected by reverse causation and is independent of confounding factors that may influence disease outcomes. Therefore, we searched PubMed, Web of Science, and the Cochrane Library databases for studies published in English from database inception to December 30, 2023, that investigated the causal relationship between alcohol consumption and dementia risk, using the terms: ("alcohol consumption", "alcohol use", or "drinking") and ("dementia", or "Alzheimer") and "mendelian randomization". Two previous two-sample MR studies showed that genetically predicted alcohol consumption was not associated with dementia. However, both analyses were based on summary-level data and traditional linear MR, the heterogeneity of different data source may diminish statistical efficacy and linear MR may yield negative results if the J-shape relationship between alcohol consumption and dementia really exists.

Added value of this study

This study employed both linear and non-linear Mendelian randomization analyses on a large sample from the UK Biobank, specifically focusing on current drinkers of White British descent. Our findings contradicted the widely reported J-shaped relationship by demonstrating a positive linear association between alcohol consumption and the incidence of dementia among current drinkers. This study highlighted that no level of alcohol consumption is safe in terms of dementia risk.

Implications of all the available evidence

MR studies clarify the causal relevance of alcohol intake with diseases by accounting for confounding biases and reversal causation in conventional epidemiological studies. The linear and non-linear MR provides evidence on linear causal harmful effects of alcohol use on dementia. This finding improves our understanding of the adverse effects of alcohol use on dementia among current drinkers.

Introduction

The estimated number of people with dementia would increase from 57.4 million globally in 2019 to 152.8 million by 2050,[1] highlighting the pressing need for effective preventive measures and public health strategies. Heavy drinking was recognized as a modifiable dementia risk factor, but the impact of light-to-moderate alcohol consumption is still under debate.[2] Ethical constraints on conducting randomized control trials in the relation between alcohol consumption and dementia leave conventional epidemiological studies prone to biases. Notably, "abstainer bias" as one of selection bias, refers to abstainers probably chose not to drink or quit drinking for health reasons, leading to biased results.[3] Furthermore, previous studies might exclude alcohol consumers with early cognitive decline signs or overlook the interaction between alcohol use and other diseases risks leading to premature mortality before dementia diagnosis. Consequently, evidence on the association between light-to-moderate drinking and dementia risk is mixed. Some studies indicate light-to-moderate drinking is associated with lower dementia risk compared to abstainers and heavy drinkers,[4,5] but others find no association.[6,7] Further, the protective association between light-to-moderate alcohol consumption and dementia might be confounded by healthier lifestyle choices prevalent among moderate drinkers or the socioeconomic factors influencing alcohol consumption patterns. Drinking behaviors are related to many lifestyle factors, which couldn't be controlled in most conventional epidemiology studies. These limitations highlighted the challenges of confounding and reverse causality in alcohol-related epidemiology studies.

Mendelian randomization (MR) analysis in genetic epidemiology studies, is similar to a "genetic randomized control trial" due to the random allocation of genotypes from parents to offspring, and thus, not affected by reverse causation and is independent of confounding factors that may influence disease outcomes.[8] Previous MR studies assessing the relationship between alcohol consumption and dementia were based on the linear assumption, which did not establish a causal connection.[9,10] Consequently, it remains unknown whether the observed negative association between alcohol consumption and dementia among the light-to-moderate drinkers is causal. Non-linear MR is an extension to standard MR that first stratifies the population based on levels of exposure, and then conducts separate linear MR analyses within each stratum.[11] To our knowledge, there is no study on the non-linear causal relation between alcohol consumption and incident risk of dementia.

This study aimed to fill this gap by conducting both linear and non-linear MR analyses within the same population-based cohort among current drinkers, aiming to test whether the observed protective effect of light-to-moderate alcohol consumption and dementia is causal. All the analyses were stratified by sex to re-

estimate the association between alcohol consumption and dementia risk.

Methods

Study design

In the present study, we first conducted a conventional epidemiology study using a multivariable Cox model with restricted cubic spline functions to explore the non-linear relationship between alcohol consumption and the risk of dementia among current drinkers. We then further applied genetic epidemiology studies with both non-linear and linear MR to investigate their potential causal relationship. All analyses were stratified by gender to account for sex-specific effects.

Study population

The UK Biobank (UKB) served as the foundation for this study, comprising a community-based cohort of over 500,000 individuals from 22 assessment centers across the United Kingdom, recruited between 2006 and 2010.[12] At baseline, participants provided informed consent and a wealth of sociodemographic, clinical, genetic, and lifestyle data, including detailed accounts of alcohol consumption. Participants were included based on completed the alcohol consumption questionnaire and available genetic data.

Ethnic information was self-reported by participants at baseline. Analyses were restricted to white British individuals to minimize potential confounding of MR analyses by genetic ancestry. We included only current alcohol drinkers for the following two reasons. First, this study aimed to provide practical implications only for drinkers, without any intention to encourage non-drinkers to consume alcohol. Second, a focus on current drinkers should limit potential selection biases and confounding, and account for significant differences in characteristics between drinkers and non-drinkers (Appendix p 5–6). Thus, individuals with zero unit/week alcohol consumption, including abstainers and current drinkers with zero consumption were excluded. Exclusions were applied for any mismatch between self-reported and genetic sex, chromosomal anomalies, and cases of prevalent dementia at baseline, leaving 313,958 participants in the final analysis (The following chart showed in Fig. 1a).

Measures of alcohol consumption

Alcohol consumption was assessed based on self-reported weekly/monthly intake of various types, including wines, beer/cider, spirits, and others. According to the National Health Service (NHS) guidelines, weekly units were defined as follows: a drink/week alcohol of wine = 1.5 units/week; a drink/week alcohol of champagne plus white wine = 1.5 units/week; a drink/week alcohol of beer/cider = 2.8 units/week; a drink/week alcohol of spirits = 1 unit/week; a drink/week alcohol of fortified wine = 1 unit/week; a drink/week alcohol of others = 1.5 units/week. Total weekly alcohol consumption was summarized across all categories. When the weekly alcohol consumption was not available, but the monthly alcohol consumption was available, divide the monthly alcohol consumption by 4.3 to convert to weekly alcohol consumption. Alcohol consumption was categorized as 'Safe' (≤14 units/week) and 'Unsafe" (>14 units/week) following Alcohol Change UK and UK Department of Health guidelines.[13]

Measures of outcome

The incidence of all-cause dementia was obtained from UKB routinely collected healthcare data, including hospital admissions and mortality records, aligned with the International Classification of Disease 10 codes, and supplemented by algorithmically defined outcomes and self-reported conditions (Appendix p 7). Utilizing the routinely collected healthcare datasets for incident dementia is reliable, with a positive predictive value (PPV) of 82.5%.[14] However, the positive predictive value for the diagnosis of dementia subtypes is less reliable, with 71% for Alzheimer's disease (AD) and 44% for vascular dementia (VD). Consequently, this study only focused on all-cause dementia, but did not distinguish AD and VD due to lower diagnostic precision with UKB data. Follow-up duration was calculated from baseline to the earliest of first dementia diagnosis, loss to follow-up, death, or censoring (2021-11-12).

Covariables

Covariates included sociodemographic and health-related variables potentially associated with dementia risk. Gender was self-reported at baseline, and any mismatches between self-reported and genetic sex were excluded to maintain consistent gender categorization. Age was divided into three categories: ≤45, (45–65], and >65 years. Education levels were detailed as higher education/vocational (including college or university degrees and other professional qualifications), secondary education (encompassing all stages of secondary education), and other. Socioeconomic status was determined using the Townsend deprivation index, segmenting the cohort into least, middle, and most deprived groups. The areas were defined in terms of administrative boundaries (encompassing England, Scotland, Wales, and Northern Ireland). For health-related variables, BMI was categorized according to WHO guidelines into underweight (<18.5), normal weight [18.5–25), overweight [25–30), and obese (≥30 kg/m^2). Smoking status, derived from self-reports, included never, former, and current smokers. Physical activity was assessed through metabolic equivalent task minutes per week, divided into insufficient, sufficient, or additional levels based on tertiles.[15] Sleep duration was classified into less than 6 h, 6–9 h, and more than

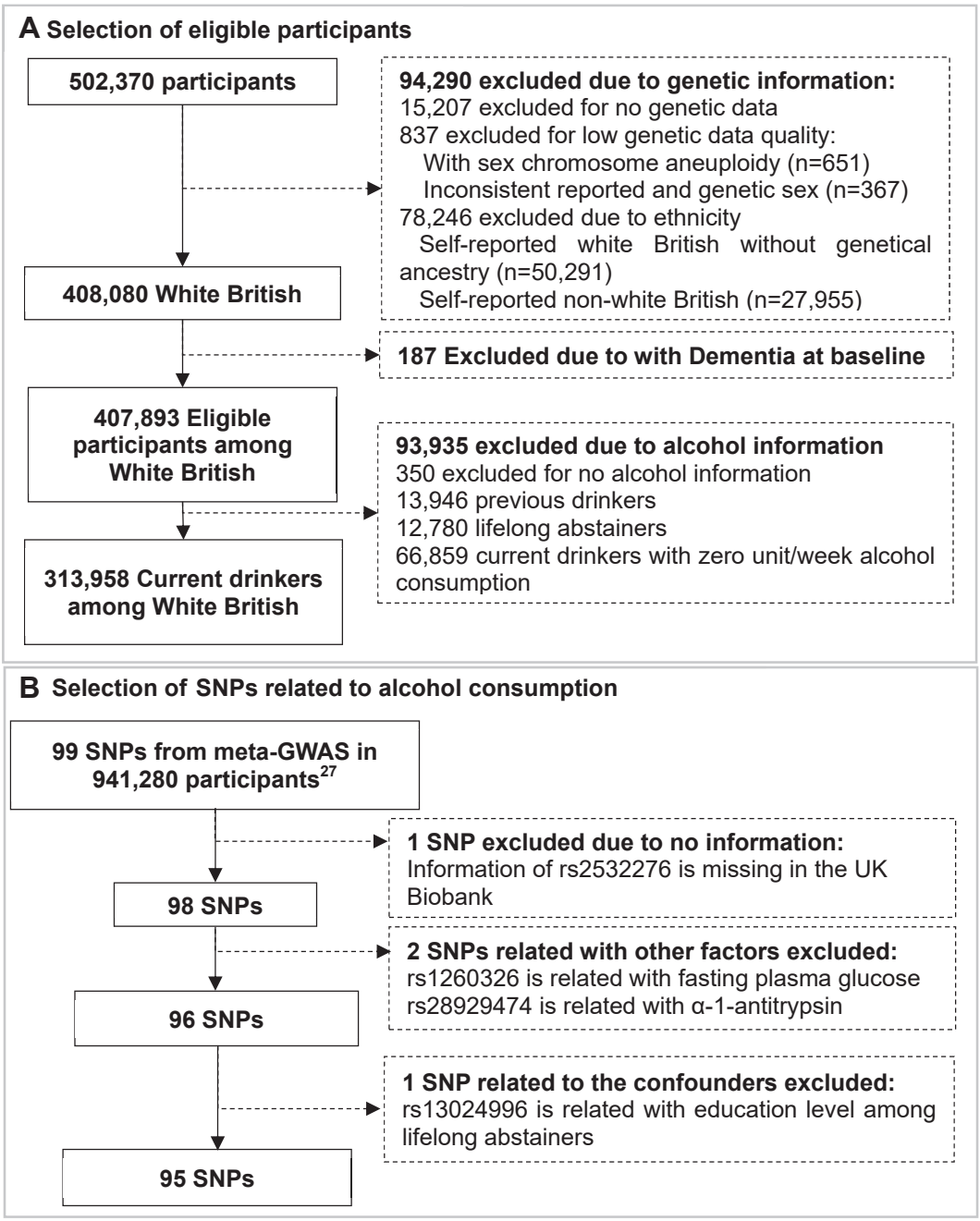

Fig. 1: **Selection of eligible participants and single nucleotide polymorphisms (SNP) of alcohol consumption in this study.**

9 h of sleep. Presence of cardiometabolic diseases (including myocardial infarction, heart failure, hypertension, and type 2 diabetes mellitus) and stroke at baseline were calculated based on UKB first occurrence or algorithm-defined outcomes.[16] Participants' APOE $\varepsilon 4$ allele status, a known genetic risk factor for dementia, was identified by the presence of one or more ε4 alleles (rs429358 and rs7412).

The genetic instrument for alcohol assumption

The alcohol consumption genetic score (Alcohol-GS) was developed as a genetic instrument by calculating a weighted genetic score based on 95 single nucleotide polymorphisms (SNPs) with their respective associations with alcohol consumption. These SNPs were selected from a comprehensive genome-wide association study (GWAS) encompassing 941,280 participants,

which identified 99 SNPs specifically linked to alcohol consumption, confirming their specificity to alcohol consumption without strong links to smoking behaviors.[17] Despite the UKB sample contributing to approximately 30% of the GWAS cohort, a weighted genetic score could potentially mitigate bias.[18] The detailed SNP selection process was shown in Fig. 1b and Appendix p 2. Each SNP was coded as 0, 1, or 2 to signify the number of alleles linked to increased alcohol consumption. Appendix p 2–3 provided details for the calculation of the Alcohol-GS and its assessment as a genetic instrument adheres to three assumptions of MR: (1) associated with alcohol consumption (log_{10} (unit/week); (2) not associated with confounders; (3) not directly associated with dementia risk. The Alcohol-GS accounted for 15.5% of the variance in log-transformed weekly alcohol consumption in the UKB, with an F-statistics of 1228.4 (Appendix p 17).

Statistics

Alcohol consumption data were log-transformed (log_{10} (unit/week)) due to their skewed distribution, with results reported in the original unit (unit/week) for clarity. The baseline characteristics of the participants were described by the mean and standard deviation (SD) for normal distributed continuous variables, the median with interquartile range (IQR) for non-normal distribution continuous variables, and proportions for categorical variables. To identify disparities between genders, standardized differences were calculated, with absolute values greater than 0.1 indicating significant differences between men and women drinkers.[19]

Initially, multivariable Cox proportional hazards models with restricted cubic spline functions were used to assess the nonlinear relationship between alcohol consumption groups and dementia incident risk. The validity of the proportional hazard assumption was confirmed using Schoenfeld residuals, with a resulting *p*-value of 0.11. The model was adjusted for sex, age, area, APOE status, education level, and socioeconomic status. For graphical representation, the alcohol consumption level associated with the lowest risk of dementia was designated as the reference point.

Subsequently, we applied non-linear MR analysis with a residual stratification method on log-transformed alcohol consumption. The normal distribution of log-transforming alcohol consumption satisfied the precondition for the residual non-linear MR. Linear MR estimations quantified localized average causal effects across ten stratified groups based on residual alcohol consumption levels. These estimates reflected the localized average causal effects within each stratum, allowing us to compare the effects of alcohol consumption across genetic backgrounds. For sensitivity analysis, we adopted the doubly-ranked stratification method, which offers a robust approach to address potential violations of constant genetic effects.[20] Furthermore, to assess the suitability of both non-linear MR methods for alcohol consumption, we utilized the established correlation between alcohol consumption and alcoholic hepatitis as a positive control, while age, which is unaffected by alcohol consumption, served as a negative control. This approach was employed to ascertain the reliability and specificity of our findings. Further details on non-linear MR analysis methods are available in Appendix p 3–4.

Given the lack of a non-linear MR association between alcohol consumption and dementia, we integrated individual-level and summary-level linear MR analyses to assess the causal effect of alcohol consumption on dementia. The individual-level analysis used Alcohol-GS as the instrument variable, aggregating the effect size of multiple SNPs to enhance the statistical power to detect associations. Conversely, the summary-level analysis directly used 95 SNPs as instruments, which could more easily assess the robust estimate and adjust for pleiotropy.

In individual-level linear MR analysis, we fitted a two-stage least-squares regression with Alcohol-GS to assess the causal relationship between alcohol consumption and dementia risk. We included death as a competing risk in a sensitivity analysis. The first stage involved linear regression to estimate alcohol consumption (log_{10} (unit/week)) from Alcohol-GS, applied with both basic and competing risk models. The second stage utilized a Cox proportional hazards model to evaluate the association between genetically estimated alcohol levels and dementia risk in the basic model, with the competing risk model further adjusted for mortality. Adjustments in both stages included age, sex, assessment centers, genotyping arrays, and the top 20 genetic principal components. While acknowledging the potential subgroup analyses to produce spurious association,[21] we aimed to evaluate the robustness of our finding and verify the consistency of the direction effect with the main result. Therefore, we conducted the subgroup analyses by age, socioeconomic status, education level, BMI, smoke status, sleep duration, physical activity level, and APOE $\varepsilon 4$ status in the sensitivity analysis.

In summary-level linear MR analysis, we obtained SNP-specific Wald estimates (quotient of genetic association on dementia and genetic association on alcohol consumption (log_{10} (unit/week)) and then meta-analyzed them using Inverse Variance Weighted (IVW) with multiplicative random effects. To address directional pleiotropy, we employed MR-Egger and the Weighted Median as sensitivity analyses. To address the potential bias of sample overlap in one sample, we implemented a 10-fold MR strategy. We further performed summary-level two-sample MR analysis as the sensitivity analysis (Appendix p 4–5).

All statistical tests were estimated by 2-sided tests. A p value less than 0.05 was considered significant. All analyses were undertaken using R.

Ethics

The UK Biobank obtained ethical approval from the Research Ethics Committee (REC reference 11/NW/0382), and all participants provided written informed consent.

Role of the funding source

The funder of the study did no participate in the design of study, the collection, analysis, or interpretation of data, the writing of the manuscript, or the decision to submit the manuscript for publication.

Results

Baseline characteristic

Out of 313,958 current drinkers, 5394 individuals (1.7%) were diagnosed with dementia during an average follow-up year of 13.2 years (SD 2.0). The median weekly alcohol consumption was 13.60 units (IQR 7.10–25.20). About half of current drinkers (48.6%) exceed the UK's recommended alcohol intake threshold of 14 units per week. Additionally, the cohort showed a balanced gender distribution, but women represented the double proportion of men in the safe alcohol consumption group, the pattern reversed in the unsafe alcohol consumption group (Table 1).

Findings from restricted cubic spline Cox Proportional Hazards analyses

The multivariable Cox Proportional Hazards analyses with restricted cubic spline functions revealed a J-shaped relationship between alcohol consumption and dementia risk among overall current drinkers, with a significant non-linear test ($p = 0.04$) (Fig. 2). The lowest dementia risk was observed at an alcohol consumption level of 11.9 units/week, which was smaller than the recommended threshold of 14 units/week. A similar J-shape pattern appeared for men, with the lowest dementia risk at 16.8 units/week ($p = 0.04$). While for women, the analysis did not reveal a significant non-linear relationship, with minimal risk observed at 8.4 units/week.

Findings from non-linear mendelian randomization analyses

The non-linear MR analysis showed no significant deviation from a linear relationship between genetically predicted alcohol and dementia risk in the overall current drinkers (Non-linear test of $p = 0.45$). However, a significant positive correlation was identified ($p = 0.02$), with no significant heterogeneity (Cochran Q $p = 0.34$; Fig. 3). Sensitivity analyses applying the double-rankly stratification non-linear MR showed a similar result (Appendix p 22). Appendix p 18 showed significant associations between Alcohol-GS and alcohol consumption across the strata by both non-linear MR methods.

In gender-specific analysis, no significant non-linear correlation was observed between genetic alcohol consumption and dementia risk in either men or women (p for non-linear test were 1.00 in men and 0.20 in women) (Fig. 3). Men did not exhibit a statistically significant genetic correlation with dementia risk ($p = 0.43$ and Cochran Q $p = 0.83$). Conversely, women showed a significant positive association but with significant heterogeneity ($p = 0.005$ and Cochran Q $p = 0.01$).

In sensitivity analyses, the positive control confirmed a strong positive correlation ($p < 0.001$) between genetically predicted alcohol consumption and alcoholic liver disease, without evidence of non-linearity or significant heterogeneity. The negative control analysis showed no significant association between genetically predicted alcohol consumption and age. All these results reinforced the reliability and specificity of the non-linear MR analysis (Appendix p 23–24).

Findings from linear mendelian randomization analyses

The individual-level linear MR analysis provided robust evidence that an increasing genetically predicted alcohol consumption was associated with an increased risk of dementia (HR 2.22 [95% CI 1.06–4.66]) among overall drinkers. Further analysis considering competing risk events confirmed the causal genetic relationship (3.78 [1.33–10.8]; Table 2). Subgroup sensitivity analyses revealed consistent positive correlations across various strata between genetically predicted alcohol consumption and dementia risk (Appendix p 19).

Summary-level linear MR as complementary analysis identified similar findings, the effect estimates were broadly consistent between IVW (HR 1.89 [95% CI 1.53–2.32]) and the pleiotropy robust methods as MR-egger (2.35 [1.73–3.23]) and weighted median (2.41 [1.76–3.30]) in one-sample MR with a 10-fold method to overcome the overfitting. For sensitivity analysis, we further conducted the two-sample summary-level MR from two independent studies to test the robustness of the MR estimates (Appendix p 20). IVW method yielded similar findings (1.62 [1.08–2.44]), the other two MR methods did not reach statistical significance (MR-egger: 1.60 [0.70–3.68]; weighted median MR: 1.67 [0.91–3.07]). However, they maintained the same directional effect between genetically predicted alcohol consumption and dementia risk, suggesting a coherent pattern. Additionally, MR-Egger analysis in this context also found no evidence of pleiotropy among drinkers, reinforcing the absence of bias in our observed associations.

Linear MR analyses underscored a positive genetic linkage in women (HR 3.25 [95% CI 0.98–10.8]), which was further affirmed in analyses considering competing

risks (7.73 [1.47–40.7]). Although the results for the men were not statistically significant, the direction of effect was consistent with the results among overall drinkers. Summary-level MR analyses confirm a positive link between genetically predicted alcohol intake and dementia risk across genders (Table 2).

Discussion

The conventional epidemiology analysis showed a J-shaped association between alcohol consumption and dementia among current drinkers. Nevertheless, the non-linear MR analysis did not detect the non-linear causal relationship between genetically predicted alcohol consumption and the risk of dementia. The linear MR analysis identified a linear causal relationship between alcohol consumption and dementia among the current drinkers.

In multivariable Cox regression analyses, we found that the moderate alcohol consumption group exhibited a protective effect with the risk of dementia, compared with the light alcohol consumption group, and the non-linear model result indicated a J-shaped association between alcohol consumption and the occurrence of dementia among current drinkers. These results are similar to findings from the most comprehensive and recent meta-analyses in conventional epidemiological studies.[4,5,22] However, none of the studies recommended the abstainers to drink for the prevention of dementia, because these conventional studies are susceptible to selection biases, confounding, and reverse causality and alcohol drinking may lead to also other health problems. Moderate drinkers might practice principles of moderation in other areas of life that live a healthier life than others,[23] while abstinence might indicate withdrawal from leisure activities that were not beneficial for preventing cognitive decline.[24] In particular, socioeconomic status influenced the amount and type of alcohol consumed, and as such, might play an important confounding role in the alcohol-dementia relationship.[25] As mentioned before, a major bias in alcohol epidemiology is the "abstainer bias", referring to the phenomenon that abstainers probably choose not to drink or quit drinking for health reasons. Therefore, the abstainer group may have worse health status than the light-to-moderate drinkers. To account for this bias, lifetime abstainers were used as a reference group against drinkers. However, as young adults who have a limiting long-standing illness are more likely not to drink alcohol, the life-time abstainers might also be very different from drinkers.[26] This discrepancy can lead to an exaggerated perception of the protective benefits of light-to-moderate drinking. Addressing abstainer bias, a study focusing on current alcohol drinkers found a negative association between alcohol consumption and cognitive function in a dose–response manner.[27] This study highlighted the potential overestimation of protective effects in conventional epidemiology research. Despite this study's focus on current drinkers to mitigate "abstainer bias", MR analysis provided a supplementary viewpoint to assess the relationship between alcohol consumption and health outcomes. A recent study presented findings indicat65ing the

	Overall	Men	Women	SMD[a]
No of participant	313,958	157,087 (50.03)	156,871 (49.97)	
Follow-up years, year[b]	13.2 ± 2.0	13.1 ± 2.2	13.3 ± 1.7	0.12
Alcohol consumption, unit/week[c]	13.6 [7.1, 25.2]	20.2 [11.2, 33.9]	9.5 [5.3, 16.7]	0.40
Alcohol intake, n (%)				
≤14 units/week	161,314 (51.4)	53,751 (34.2)	107,563 (68.6)	0.69
>14 units/week	152,644 (48.6)	103,336 (65.8)	49,308 (31.4)	0.69
Age, year[b]	56.8 ± 8.0	56.5 ± 7.9	56.5 ± 7.9	0.09
Age group, n (%)				
≤45 year	37,029 (11.8)	18,116 (11.5)	18,913 (12.1)	0.02
(45, 65] year	230,583 (73.4)	113,167 (72.0)	117,416 (74.8)	0.06
>65 year	46,346 (14.8)	25,804 (16.4)	20,542 (13.1)	0.09
Socioeconomic, n (%)				
Least deprived	70,585 (22.5)	35,096 (22.3)	35,489 (22.6)	0.01
Middle deprived	195,329 (62.2)	96,744 (61.6)	98,585 (62.8)	0.03
Most deprived	48,044 (15.3)	25,247 (16.1)	22,797 (14.5)	0.04
Education, n (%)				
Higher or vocational	174,251 (55.5)	91,223 (58.1)	83,028 (52.9)	0.10
Upper or lower secondary	77,536 (24.7)	33,901 (21.6)	43,635 (27.8)	0.14
Other	62,171 (19.8)	31,963 (20.3)	30,208 (19.3)	0.03
BMI group, n (%)				
<18.5 kg/m^2	1360 (0.4)	304 (0.2)	1056 (0.7)	0.07
[18.5–25.0] kg/m^2	104,510 (33.4)	38,749 (24.7)	65,761 (42.0)	0.37
[25.0–30.0] kg/m^2	138,200 (44.1)	79,415 (50.7)	58,785 (37.6)	0.26
≥30.0 kg/m^2	69,036 (22.0)	38,157 (24.4)	30,879 (19.7)	0.11
Smoke status, n (%)				
Never	165,461 (52.9)	75,310 (48.1)	90,151 (57.6)	0.19
Previous	117,005 (37.4)	63,475 (40.5)	53,530 (34.2)	0.13
Current	30,520 (9.8)	17,808 (11.4)	12,712 (8.1)	0.11
Sleep duration group, n (%)				
<6 h	13,995 (4.5)	6813 (4.3)	7182 (4.6)	0.01
[6–9] hour	295,388 (94.1)	147,972 (94.2)	147,416 (94.0)	0.01
>9 h	4575 (1.5)	2302 (1.5)	2273 (1.4)	0.00
Physical activity, n (%)				
Insufficient	83,046 (32.1)	42,499 (31.7)	40,547 (32.5)	0.03
Sufficient	88,196 (34.1)	44,462 (33.1)	43,734 (35.1)	0.01
Additional	87,723 (33.9)	47,298 (35.2)	40,425 (32.4)	0.10
Comorbid disease at baseline, n (%)				
Cardiometabolic disease	88,089 (28.1)	34,792 (22.2)	53,297 (33.9)	0.26
Stroke	4220 (1.3)	1469 (0.9)	2751 (1.8)	0.07
APOE $\varepsilon 4$, n (%)				
Without	231,429 (73.7)	115,751 (73.7)	115,678 (73.7)	0.00
With	82,529 (26.3)	41,336 (26.3)	41,193 (26.3)	0.00

[a]SMD was standardized difference, employed to assess differences between female and male drinkers, with values exceeding 0.1 considered significant. [b]The follow-up year showed in mean ± standard deviation. [c]Alcohol consumption showed the median [P_{25}, P_{75}].

Table 1: **Baseline characteristics of overall current drinkers and comparisons between men and women drinkers.**

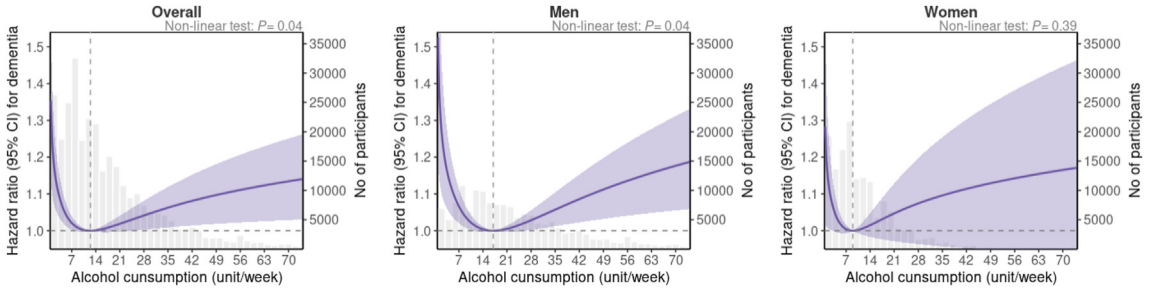

Fig. 2: **Association between alcohol consumption per week and dementia incidence risk among current drinkers.** The analyses were adjusted for demographic and genetic factors, including age, area, socioeconomic status, education level, and the presence of the APOE ε4 allele. The 95% confidence interval is indicated by the shaded region. A J-shaped association is apparent for both the overall cohort and male drinkers, with a non-linear test *p*-value of 0.04 in each, suggesting a statistically significant pattern. Reference levels of alcohol consumption were 11.94 units/week for all current drinkers, 16.60 units/week for men, and 8.39 units/week for women. Dashed lines represent the reference levels and lowest level of alcohol consumption for dementia risk in each models.

absence of genetic evidence for a net protective effect of moderate alcohol consumption on cardiovascular mortality, despite the presence of a J-shaped association in conventional epidemiological analysis.[28]

Our non-linear MR results could not provide any evidence to support a non-linear association between alcohol consumption and the incidence of dementia among current drinkers. The "instrument-free" residual strata nonlinear MR could assess the shape of the causal relationship between an exposure and outcome using individual-level data,[11] which has been applied to confirm the J-shaped relationship between BMI and cardiovascular disease mortality.[29] To avoid the collider bias from simply stratifying on measure exposure, the "instrument-free" residual strata nonlinear MR calculates the residuals from regression on measure exposure on the genetic instrument and undertaking MR analyses in strata, then evaluates the heterogeneity of the results among the strata and perform a test for nonlinear relationships. Although it is argued that there may be some problems with this nonlinear MR method when exploring the relationship between vitamin D and mortality.[20,30] The reason was the residual nonlinear MR defaults to the distribution of the measured exposure satisfying a normal distribution to fitting regression model on the exposure and the genetic instrument. So, the estimates with this method were biased when vitamin D distribution was significantly skewed. A new nonlinear MR with double ranked strata method was used to deal with the non-normal distribution of exposure.[31] The doubly ranked non-linear MR involves ranking individuals based on the residuals from a regression of the exposure on the genetic instrument, thus creating strata without the need for strict parametric assumptions about the relationship between the instrument and the exposure. This process ensures that within each stratum, the instrumental variable assumptions hold true, facilitating a more reliable exploration of non-linear or heterogeneous effects.[31] Moreover, in our study, we also used alcohol-related

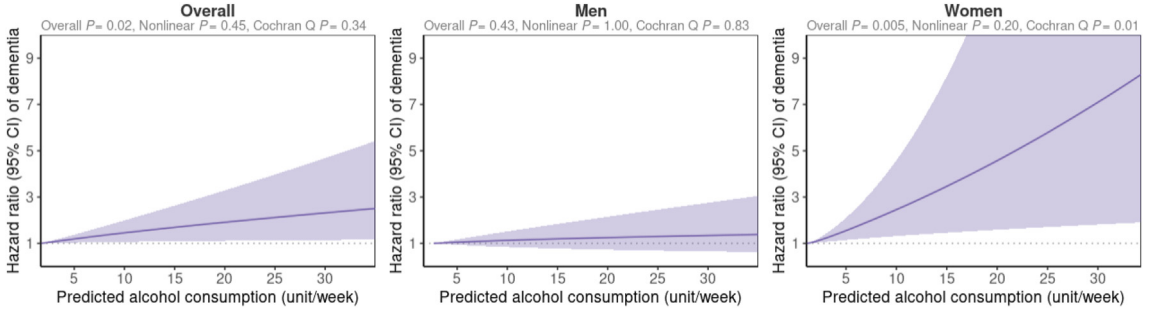

Fig. 3: **Association between genetically predicted alcohol consumption per week and dementia incident risk using non-linear mendelian randomization analysis among current drinkers.** The study utilized a residual-based fractional polynomial method to assess the causal effect of alcohol consumption on dementia risk by stratifying the sample into 10 groups. The localized average causal effect was determined by examining the gradient at each point on the curve, with shaded areas representing 95% confidence intervals. The association between genetically predicted alcohol consumption and dementia risk was statistically evaluated using the overall *p*-value, while heterogeneity across strata was assessed using the Cochran Q *p*-value. A random-effects model was applied if the Cochran Q *p*-value was less than 0.05.

liver disease and age as positive and negative control outcomes to confirm both available residual strata and doubly ranked strata nonlinear MR to verify the causal relationship between alcohol consumption and dementia.

We further performed linear MR analysis and confirmed the linear causal relationship between genetically predicted alcohol consumption and dementia among current drinkers, especially among the women drinkers. This results is inconsistent with previous two-sample MR research showed that genetically predicted alcohol consumption was not associated with dementia.[10,32] One MR study extracted 99 SNPs for alcohol consumption from the same meta-GWAS with our study, but only 41f SNP for MR analysis after a series of refinements, including clumping, proxy searching, and harmonizing SNPs associated with dementia from a meta-GWAS including 17,008 cases and 371,154 controls.[32] This decrease may lead to a less comprehensive capture of the genetic predisposition to alcohol consumption, potentially affecting the strength and accuracy of the MR analysis. Another only included three SNPs in MR analysis,[10] which may lead to an underpowered statistical estimation and a high possibility of false-negative outcomes. Both of these analyses were based on summary-level data, the heterogeneity of different data source may also diminish statistical efficacy. Contrastingly, a recent MR study aligned with our findings, suggesting that any level of alcohol consumption adversely affected brain health and was unlikely to mitigate Alzheimer's Disease risk.[32] Our findings reinforce comprehensive linear MR analyses, incorporating individual-level MR to boost statistical power and summary-level MR to mitigate overfitting and bias from sample overlap. These approaches addressed the heterogeneity and potential biases, providing a robust foundation for our conclusions. This multifaceted approach solidified the evidence base, affirming alcohol consumption's detrimental effects on dementia risk across different methodological frameworks.

Our analyses found a distinctly more significant association between alcohol consumption and dementia risk among women drinkers, a finding that can be partially explained by the component cause model.[33] The 2020 Lancet Commission's identification of various dementia risk factors, such as hypertension and smoking.[2] Studies indicated that an integrative healthier lifestyle (non-smoking, less alcohol consumption, adequate sleep, physical activity, and a balanced diet) could prevent dementia.[34] The component cause model posits that diseases like dementia result from various risk factors combined to form a sufficient cause. This framework suggested that alcohol's impact on dementia may be more evident in women, who typically had lower rates of other risk factors, such as smoking, compared to men. For men, the presence of multiple risk factors could mask alcohol's specific effects. A review discusses differences in susceptibility to dementia based on lifestyle factors like smoking, excessive alcohol use, and poor diet, further emphasizing the importance of a comprehensive approach to understanding and addressing the risk factors for dementia.[35] It points out that the impact of health conditions on dementia risk can vary by sex, with women being at a greater risk for Alzheimer's disease and men for vascular dementia. A recent study provided updated estimates on the proportion of Alzheimer's and related dementias in the US related to modifiable risk factors.[36] It also assessed differences by sex, finding that the combined population-attributable risks were higher in men than in women and varied by race and ethnicity.

Although many studies have found a negative association between light-to-moderate alcohol consumption and dementia incidence, none of the hypothesized mechanisms explaining this phenomenon has been proved.[37] Presuming the observed benefits of alcohol consumption on cognitive health still existed after all the biases were addressed, the benefits may still not be the result of ethanol but other constituents in alcoholic beverages, such as flavonoids, resveratrol, and polyphenols.[38] The specific beneficial elements, if there are any, should be investigated and promoted instead of alcohol use in general. Ethanol and acetaldehyde (a

	Overall		Men		Women	
	Predictive hazard ratio (95% CI)	*p*	Predictive hazard ratio (95% CI)	*p*	Predictive hazard ratio (95% CI)	*p*
Individual-level analyses[a]						
Basic model	2.22 (1.06–4.66)	0.04	1.74 (0.69–4.44)	0.24	3.25 (0.98–10.8)	0.05
Competing risk model	3.78 (1.33–10.8)	0.01	2.21 (0.59–8.30)	0.24	7.73 (1.47–40.7)	0.02
Summary-level analyses[b]						
Inverse variance weighted	1.89 (1.53–2.32)	<0.001	1.52 (1.24,1.86)	<0.001	1.83 (1.41,2.36)	<0.001
MR-egger[c]	2.35 (1.73–3.23)	<0.001	2.08 (1.54,2.83)	<0.001	1.74 (1.18,2.57)	0.005
Weighted median	2.41 (1.76–3.30)	<0.001	1.64 (1.19,2.24)	0.002	2.13 (1.41,3.21)	<0.001

[a]Individual-level analyses used a two-stage least squares regression, employing Alcohol-GS as instruments for alcohol consumption. The first stage involved linear regression to estimate alcohol consumption (log_{10} units/week) from Alcohol-GS, applied with both basic and competing risk models. The second stage utilized a Cox proportional hazards model to evaluate the association between genetically estimated alcohol levels and dementia risk in the basic model, with the competing risk model further adjusted for mortality. Adjustments in both stages included age, sex, assessment centers, genotyping arrays, and the top 20 genetic principal components. [b]Summary-level analysis employed instrumental variable (IV) methods, including Inverse Variance Weighted (IVW), MR-Egger, and Weighted Median, using 95 SNPs related to alcohol consumption as instruments. A 10-fold MR strategy was used by randomly dividing the UK Biobank (UKB) data into ten subsets. Each subset was sequentially used to fit the SNPs to alcohol consumption (log_{10} units/week) through linear regression, while the other nine subsets were pooled for fitting SNPs to dementia risk with a Cox proportional hazards model. Adjustments for age, sex, assessment centers, genotyping arrays, and the top 20 genetic principal components were made in both models. The results from these iterations were meta-analyzed to estimate the causal effect. [c]The MR-Egger regression intercepts did not provide evidence of horizontal pleiotropy in overall (beta (se) = −0.002 (0.02), p = 0.12) and women (beta = −0.0001 (0.002), p = 0.27), but indicated horizontal pleiotropy in men (beta (se) = −0.004 (0.001), p = 0.004).

Table 2: **Linear mendelian randomization analysis for the association between genetically predicted log-transform alcohol consumption with dementia risk in current drinkers.**

metabolite) are neurotoxic and cause central nervous system inflammation, reduced numbers, and morphological changes in hippocampal neurons in animal models.[39] Alcohol can also induce brain atrophy with neuronal loss, particularly in the frontal cortex,[40] central nervous system inflammation and epilepsy, all of which contribute to dementia risk.[41] In a 30-year longitudinal study, multimodal magnetic resonance imaging (MRI) showed that even moderate alcohol intake was associated with adverse brain outcomes including hippocampal atrophy and impaired white matter microstructure.[42] In addition, the effect of alcohol on dementia can be indirect through diseases linked to higher intake of alcohol and dementia, such as liver and kidney disease, diabetes, hypertension, coronary heart disease, and stroke.[43–46] Therefore, research findings concerning alcohol use need to be interpreted with caution, as certain conclusions favoring alcohol use may bring about negative impact on population health in the long run. Based on the most updated evidence, we tend to believe that there is no safe level of alcohol consumption for dementia.

We used a MR study design to assess the causal associations between genetically predicted alcohol consumption and dementia among current drinkers. This design could minimize the potential biases due to confounding and reverse causality in conventional epidemiology analyses. Application of both linear and non-linear MR analyses allows for a comprehensive assessment of the relationship, including the exploration of potential non-linear effects, thereby addressing the debated protective impact of light-to-moderate alcohol consumption on dementia risk. Consistent findings across linear and nonlinear MR analyses strengthened the evidence for the causal adverse effects of genetically predicted alcohol consumption and all-cause dementia.

The results of this study should be interpreted in conjunction with some limitations. First, our study was the reliance on self-reported alcohol consumption, which might introduce bias. Although self-reported data may be prone to recall inaccuracies, evidence indicates that such errors do not markedly undermine the validity of genetic epidemiological associations. A study in the UK Biobank found significant genome-wide associations for self-reported alcohol consumption, suggesting a genetic basis for these self-reports and implicating genes involved in alcohol metabolism and neurobiology of substance use.[47] Second, another limitation to consider was the change in alcohol consumption over time. Previous research using data from the Whitehall II project explored the relationship between changes in alcohol consumption and dementia risk, finding results consistent with studies based on a single time point measurement.[22] This consistency suggested that although alcohol consumption patterns may change over time, the impact on dementia risk remained significant, supporting the relevance of our findings. Third, the use of dementia diagnoses derived from electronic health records could be seen as a limitation, given the potential for misclassification. However, only if under recording occurred more in participants who drink less, the association observed in this study would be overestimated. We found no evidence to support this assumption. Fourth, UKB was selective, participants were early-late-life people of European ancestry with higher average levels of educational attainment and general health. However, in this study, we performed sensitivity analyzes that demonstrated the robustness of our findings. At the same time, many associations observed in other studies could be replicated in the UK Biobank, suggesting that selection bias, if existent in this study, is not greater than that in others. This study identifies a positive linear causal relationship between alcohol consumption and dementia among current drinkers. However, their J-shaped association found in observational studies is not supported by non-linear Mendelian randomization analyses. The lower risk of dementia observed among the light-to-moderate alcohol drinkers may be due to several epidemiological biases. We tend to believe that there is no safe level of alcohol consumption for dementia among current drinkers. And our study's focus on White British individuals for reducing genetic confounding, limits the generalizability to other racial and ethnic groups. Future research should include more diverse populations to better understand the implications of alcohol consumption on dementia risk. Finally, our analysis was restricted to current drinkers, which may limit the generalizability of our findings. By excluding non-drinkers and former drinkers, we focused on a more homogeneous study population, aiming to reduce variability and potential confounding factors related to past drinking behaviors. However, this approach means our results may not be applicable to those who have never consumed alcohol or who have quit drinking due to health reasons or other factors. Our findings are intended to inform current drinking behaviors and we do not aim to give any suggestions to non-drinkers.

Contributors

FS, LLZ and WYL contributed to study conception and design, with development of genetic risk scores and statistical analysis led by JLT and ZGG. FS and LLZ accessed and verified the underlying data. LLZ carried out primary data analysis. LLZ completed the statistical analysis under supervision of FS, JLT, and ZGG. JLT, and ZGG supervised the project. FS, LLZ and WYL wrote the first draft of the manuscript. All authors contributed to critical revision and editing of the manuscript, and have approved the final version. JLT, FS and LLZ were responsible for the decision to submit the manuscript. FS, LLZ and WYL contributed equally, and are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing statement

The current study was conducted using the UK Biobank resource under application No. 80476. All raw and derived data in this study are available from the UK Biobank (http://www.ukbiobank.ac.uk/).

Declaration of interests
All authors declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102810.

References
1 GBDDF Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105–e125.
2 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413–446.
3 Rehm J, Spuhler T. Measurement error in alcohol consumption: the Swiss Health Survey. *Eur J Clin Nutr*. 1993;47(Suppl 2):S25–S30.
4 Liu Y, Mitsuhashi T, Yamakawa M, et al. Alcohol consumption and incident dementia in older Japanese adults: the Okayama Study. *Geriatr Gerontol Int*. 2019;19(8):740–746.
5 Jeon KH, Han K, Jeong SM, et al. Changes in alcohol consumption and risk of dementia in a nationwide cohort in South Korea. *JAMA Netw Open*. 2023;6(2):e2254771.
6 Heffernan M, Mather KA, Xu J, et al. Alcohol consumption and incident dementia: evidence from the sydney memory and ageing study. *J Alzheimers Dis*. 2016;52(2):529–538.
7 Langballe EM, Ask H, Holmen J, et al. Alcohol consumption and risk of dementia up to 27 years later in a large, population-based sample: the HUNT study, Norway. *Eur J Epidemiol*. 2015;30(9):1049–1056.
8 Davey Smith G, Ebrahim S. What can mendelian randomisation tell us about modifiable behavioural and environmental exposures? *BMJ*. 2005;330(7499):1076–1079.
9 Luo J, Thomassen JQ, Bellenguez C, et al. Genetic associations between modifiable risk factors and alzheimer disease. *JAMA Netw Open*. 2023;6(5):e2313734.
10 Larsson SC, Traylor M, Malik R, Dichgans M, Burgess S, Markus HS. Modifiable pathways in Alzheimer's disease: mendelian randomisation analysis. *BMJ*. 2017;359:j5375.
11 Staley JR, Burgess S. Semiparametric methods for estimation of a nonlinear exposure-outcome relationship using instrumental variables with application to Mendelian randomization. *Genet Epidemiol*. 2017;41(4):341–352.
12 Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.
13 NHS. *The risks of drinking too much*; 2022. https://www.nhs.uk/live-well/alcohol-advice/the-risks-of-drinking-too-much/.
14 Wilkinson T, Schnier C, Bush K, et al. Identifying dementia outcomes in UK Biobank: a validation study of primary care, hospital admissions and mortality data. *Eur J Epidemiol*. 2019;34(6):557–565.
15 Li J, Zheng L, Chan KHK, et al. Sex hormone-binding globulin and risk of coronary heart disease in men and women. *Clin Chem*. 2023;69(4):374–385.
16 Yun Q, Wang S, Chen S, et al. Constipation preceding depression: a population-based cohort study. *EClinicalMedicine*. 2024;67:102371.
17 Liu MZ, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet*. 2019;51(2):237–244.
18 Fang S, Hemani G, Richardson TG, Gaunt TR, Davey Smith G. Evaluating and implementing block jackknife resampling Mendelian randomization to mitigate bias induced by overlapping samples. *Hum Mol Genet*. 2023;32(2):192–203.
19 Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ*. 2005;330(7497):960–962.
20 Burgess S, Wood AM, Butterworth AS. Mendelian randomisation and vitamin D: the importance of model assumptions - authors' reply. *Lancet Diabetes Endocrinol*. 2023;11(1):15–16.
21 Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. *BMJ*. 2018;362:k601.
22 Sabia S, Fayosse A, Dumurgier J, et al. Alcohol consumption and risk of dementia: 23 year follow-up of Whitehall II cohort study. *BMJ*. 2018;362:k2927.
23 Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in the elderly: a systematic review. *Age Ageing*. 2008;37(5):505–512.
24 Li B, Bi J, Wei C, Sha F. Specific activities and the trajectories of cognitive decline among middle-aged and older adults: a five-year longitudinal cohort study. *J Alzheimers Dis*. 2021;80(3):1039–1050.
25 Collins SE. Associations between socioeconomic factors and alcohol outcomes. *Alcohol Res Curr Rev*. 2016;38(1):83–94.
26 Ng Fat L, Shelton N. Associations between self-reported illness and non-drinking in young adults. *Addiction*. 2012;107(9):1612–1620.
27 Hassing LB. Light alcohol consumption does not protect cognitive function: a longitudinal prospective study. *Front Aging Neurosci*. 2018;10:81.
28 Millwood IY, Im PK, Bennett D, et al. Alcohol intake and cause-specific mortality: conventional and genetic evidence in a prospective cohort study of 512 000 adults in China. *Lancet Public Health*. 2023;8(12):e956–e967.
29 Sun YQ, Burgess S, Staley JR, et al. Body mass index and all cause mortality in HUNT and UK Biobank studies: linear and non-linear mendelian randomisation analyses. *BMJ*. 2019;364:l1042.
30 Wade KH, Hamilton FW, Carslake D, Sattar N, Davey Smith G, Timpson NJ. Challenges in undertaking nonlinear Mendelian randomization. *Obesity*. 2023;31(12):2887–2890.
31 Tian H, Mason AM, Liu C, Burgess S. Relaxing parametric assumptions for non-linear Mendelian randomization using a doubly-ranked stratification method. *PLoS Genet*. 2023;19(6):e1010823.
32 Andrews SJ, Goate A, Anstey KJ. Association between alcohol consumption and Alzheimer's disease: a Mendelian randomization study. *Alzheimers Dement*. 2020;16(2):345–353.
33 Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
34 Ward DD, Ranson JM, Wallace LMK, Llewellyn DJ, Rockwood K. Frailty, lifestyle, genetics and dementia risk. *J Neurol Neurosurg Psychiatry*. 2022;93(4):343–350.
35 Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci*. 2016;18(4):437–446.
36 Nianogo RA, Rosenwohl-Mack A, Yaffe K, Carrasco A, Hoffmann CM, Barnes DE. Risk factors associated with alzheimer disease and related dementias by sex and race and ethnicity in the US. *JAMA Neurol*. 2022;79(6):584–591.
37 Wiegmann C, Mick I, Brandl EJ, Heinz A, Gutwinski S. Alcohol and dementia - what is the link? A systematic review. *Neuropsychiatr Dis Treat*. 2020;16:87–99.
38 Haseeb S, Alexander B, Baranchuk A. Wine and cardiovascular health: a comprehensive review. *Circulation*. 2017;136(15):1434–1448.
39 Anton PE, Rutt LN, Kaufman ML, Busquet N, Kovacs EJ, McCullough RL. Binge ethanol exposure in advanced age elevates neuroinflammation and early indicators of neurodegeneration and cognitive impairment in female mice. *Brain Behav Immun*. 2024;116:303–316.
40 Harper C. The neuropathology of alcohol-related brain damage. *Alcohol Alcohol*. 2009;44(2):136–140.
41 Samokhvalov AV, Irving H, Mohapatra S, Rehm J. Alcohol consumption, unprovoked seizures, and epilepsy: a systematic review and meta-analysis. *Epilepsia*. 2010;51(7):1177–1184.
42 Topiwala A, Allan CL, Valkanova V, et al. Moderate alcohol consumption as risk factor for adverse brain outcomes and cognitive decline: longitudinal cohort study. *BMJ*. 2017;357:j2353.

43 Berger I, Wu S, Masson P, et al. Cognition in chronic kidney disease: a systematic review and meta-analysis. *BMC Med*. 2016;14(1):206.
44 Kim HM, Lee YH, Han K, et al. Impact of diabetes mellitus and chronic liver disease on the incidence of dementia and all-cause mortality among patients with dementia. *Medicine (Baltimore)*. 2017;96(47):e8753.
45 Kuzma E, Lourida I, Moore SF, Levine DA, Ukoumunne OC, Llewellyn DJ. Stroke and dementia risk: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14(11):1416–1426.
46 Wolters FJ, Segufa RA, Darweesh SKL, et al. Coronary heart disease, heart failure, and the risk of dementia: a systematic review and meta-analysis. *Alzheimers Dement*. 2018;14(11):1493–1504.
47 Clarke TK, Adams MJ, Davies G, et al. Genome-wide association study of alcohol consumption and genetic overlap with other health-related traits in UK Biobank (N=112 117). *Mol Psychiatry*. 2017;22(10):1376–1384.